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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,581	03/18/2002	E. Premkumar Reddy	6056-268	5000

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/018,581	REDDY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 2-14 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 11-14-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figure 4 depicts two sets of bars. One set is associated with a – sign and another set is associated with a + sign. The figure description fails to explain as to what represents these signs. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-5, are drawn to a method of screening a test substance for COX-2 inhibitory activity comprising, contacting the test substance with indicator cells (as well as

control cells) which express a GTPase-deficient mutant form of Gα12 (Gα12QL) wherein said mutant has the capacity to induce the production of arachidonic acid as well as induce the expression of COX-2 and determining level of proliferation of the indicator cells, wherein a decrease in the proliferation indicates that the test substance has COX-2 inhibitory activity.

However, said claims are still not clear to the Examiner for the following reasons. A perusal of the literature in the art as well as the specification (see p 2, lines 26-29) indicates that cells that have been transfected with just the mutant αG12QL renders them highly proliferative and such cells indeed become oncogenic (see Xu et al. PNAS 1993, Vol. 90:6741-45). Thus, even before the effects of COX-2 --that is also induced by the above mutant—can be seen, the cells are rendered proliferative by αG12QL mutant. Therefore, basing an assay for detection of inhibitory compound against COX-2 activity by determining cell proliferation may not actually lead to such compounds, rather would yield compounds that inhibit the activity of the mutant αG12QL. Unless applicants provide an assay to differentiate the proliferative activity induced by the mutant αG12QL and the proliferative activity induced specifically by COX-2, compounds that inhibit proliferation of indicator cells may not provide compounds that actually inhibit COX-2.

In response to the previous Office action, applicants have traversed the previous rejection. Applicants have also cancelled claim 1 and amended claim 2 by providing the limitation of using a control set. However, while such amendments and arguments appear to have overcome the previous rejection, claims 2-4 remain unclear for the reasons indicated above.

Claims 11-14, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 11-14 are drawn to a method of screening a test substance for COX-2 inhibitory activity comprising, contacting the test substance with indicator cells (as well as control cells) which express a GTPase-deficient mutant form of Gα12 (Gα12QL) wherein said mutant has the capacity to induce the production of arachidonic acid as well as induce the expression of COX-2 and determining the level of accumulation of arachidonic acid (claims 11-14), wherein an increase in the accumulation of arachidonic acid is indicative that the test substance has COX-2 inhibitory activity.

Here again the claims are confusing for the following reasons. A perusal of the literature in the art indicates that cells that have been transfected with just the mutant αG12QL renders them highly proliferative and such cells also produce high levels of arachidonic acid (see Xu et al. PNAS 1993, Vol. 90:6741-45). Thus, whether the test compound inhibits COX-2 or not will not be known due to the increase in the levels of arachidonic acid maintained by the mutant G protein. This is because the test compound may in fact not affect COX-2 at all but the cells will continue to have increased levels of arachidonic acid. Here again unless applicants provide a basis for differentiating the arachidonic acid that accumulates just due to the effects of mutant G protein and the arachidonic acid that accumulates by not being processed to prostaglandins by COX-2, the above method may not yield compounds that inhibit COX-2. While it may appear that the compound inhibits COX-2 due to the accumulation of arachidonic acid, the compound may be actually ineffective and those skilled in the art would be misled to believe that the

compound inhibits COX-2 just because of the increase in accumulation of arachidonic acid. Therefore Examiner continues to maintain that above claims are unclear.

Please note that Examiner has not rejected claims 6-10. This is because said claims are directed to an assay for screening COX-2 inhibitors based on determination of prostaglandin levels which is entirely controlled by COX-2 activity and not by αG12 mutant.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 6, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a test substance as a COX-2 inhibitory agent, wherein said COX-2 is induced in an indicator cell by the specific αG12 mutant, αG12QL, does not reasonably provide enablement for such a method wherein said COX-2 is induced in an indicator cell by any or all types of αG12 mutants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2, 6, and 11 are so broad as to encompass a method of screening a COX-2 inhibitor which is induced by any or all types of mutant αG12. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of types of mutants broadly encompassed by the claims. Since applicant's have taught that only a specific mutant of αG12 has the capacity to induce COX-2 expression in the indicator cells and since applicants have not taught that any or all types of mutants of αG12 can induce COX-2, those skilled in the art will require a knowledge of and guidance with regard to confirming that any or all types of mutants of α G12 have the capacity to induce COX-2 in indicator cells. However, in this case the disclosure is limited to the teaching that only a specific mutant α G12 QL has the capacity to induce the expression of COX-2 in indicator cells.. Therefore, it would require undue experimentation of the skilled artisan to determine and confirm those specific mutants that have the capacity to induce COX-2 for practicing the above method. The specification provides no guidance with regard to the making and selecting all types of mutants of αG12 that have the capacity to induce COX-2. In view of the great breadth of the claim, amount of experimentation required to determine those mutants of α G12 that induce COX-2, the lack of guidance, working examples, and unpredictability of the art in predicting that COX-2 can be induced by the any or all mutants G12, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

The specification does not support the broad scope of the claims which encompasses the use of all or any mutants of αG12 in the method, because the specification does not establish: (A) that any or all mutants of α G12 have the capability of inducing COX-2 in indicator cells just as the specific mutant α G12QL (B) regions of the protein structure which may be modified such that it is rendered capable of inducing COX-2; (C) the general tolerance of α G12 protein to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function (i.e., induce COX-2); and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method that lacks a confirmation step. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of mutant αG12 capable of inducing COX-2 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 2, 6, 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 6, and 11 are directed to a method in which modified polypeptide of αG12 having the capability of inducing COX-2 indicator cells are used. Claims 2, 6, 11 are rejected under this section of 35 USC 112 because the claims are directed to a method wherein a genus of modified polypeptide sequences of αG12, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue and fragments of the same are used. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single mutant i.e., αG12QL as capable of inducing COX-2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the modified αG12 polypeptide sequences capable of inducing COX-2 in indicator cells, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 2-5, 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2-5, are drawn to a method of screening a test substance for COX-2 inhibitory activity comprising, contacting the test substance with indicator cells (as well as control cells) which express a GTPase-deficient mutant form of Gα12 (specifically Gα12QL) wherein said mutant has the capacity to induce the production of arachidonic acid as well as induce the expression of COX-2 and determining the level of proliferation of the indicator cells, wherein a decrease in the proliferation indicates that the test substance has COX-2 inhibitory activity.

Claims 11-14 are drawn to a method of screening a test substance for COX-2 inhibitory activity comprising, contacting the test substance with indicator cells (as well as control cells) which express a GTPase-deficient mutant form of Gα12 (Gα12QL) wherein said mutant has the capacity to induce the production of arachidonic acid as well as induce the expression of COX-2 and determining the level of accumulation of arachidonic acid (claims 11-14), wherein an increase in the accumulation of arachidonic acid is indicative that the test substance has COX-2 inhibitory activity.

Examiner takes the position that claims 2-5 and 11-14 are not enabled for screening a test substance for COX-2 inhibitory activity for the following reasons. In claims 2-5 applicants do

not show a specific connection between the COX-2 activity and cell proliferation. Therefore, those skilled in the art would not know how to determine that a compound that inhibits proliferation also inhibits COX-2 activity. Applicants argue that COX-2 induced by the mutant αG12 renders the indicator cells to proliferate and therefore a decrease in the proliferation is indicative of inhibiting COX-2. However, it is well known in the art that transfection of a specific mutant αG12 such as α G12QL renders indicator cells such as NIH3T3 oncogenic or to proliferate profusely (See Delphine et al. Endocrinol., Vol. 139(6):2892 or Xu et al. both cited in the IDS). In fact applicants also recognize this in their specification (see pages 2-3). Therefore in the view of the above fact, those cells transfected with mutant α G12 would become proliferative perhaps for two reasons, 1) due to the direct effects of α G12 mutant and 2) due to the effects of the induced COX-2 (if any). Therefore when proliferation is being effected due to two factors it would be impossible for those skilled in the art to determine that the test compound that reduced or eliminated the proliferation of the cell was specifically due to inhibition of COX-2. For example, the test compound may directly effect the activity of mutant α G12 which eliminates the proliferation of cells and therefore also eliminate the induction of COX-2. Such a compound cannot be considered as an inhibitor of COX-2. Applicants have not provided any method to differentiate between the proliferation activity of mutant α G12 and that of COX-2. Determining the portion of proliferation that is specifically due to the activity of COX-2 would be undue experimentation to those skilled in the art in addition to the fact that any compound that is identified by the proliferation assay would not be the real COX-2 inhibitor.

Examiner takes the same position with respect to claims 11-14 as well. Here again the assay is based on measurement of accumulated arachidonic acid wherein an increase in arachidonic acid levels indicate inhibition of COX-2. It is well established in the art that cells transfected with mutant form of α G12 exhibit accumulation of large amounts of arachidonic acid (see Xu et al.). While it is well known that COX-2 further converts such arachidonic acid

to prostaglandins, basing an assay for determination of COX-2 inhibitors by measuring the accumulated arachidonic acid would be misleading. This is because, applicants have not taught how to differentiate between the test compound's action of inhibition of COX and enhancement of the activity of mutant αG12. In the assay claimed in claims 11-14, the test compound may have no effect on the induced COX at all but may indeed enhance the activity of mutant αG12 leading to large amount of arachidonic acid accumulation leading one to believe that said compound inhibits COX-2. Therefore it would be an undue burden to those skilled in the art to determine whether said compound actually has an enhancing effect on the transfected mutant α G12 or whether the compound had actually inhibited COX-2.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. Without sufficient guidance, determination of compounds that inhibit COX-2 based on the assays claimed in the claims 2-5 and 11-14 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

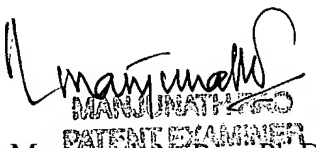
None of the claims are allowable.

Examiner has withdrawn the previous rejections under 35 U.S.C. 102(b) and 103(a) in view of claim amendments and arguments provided by the applicant.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao, Ph.D.
February 6, 2004